

## REVIEW

# Squeezing the antibiotic balloon: the impact of antimicrobial classes on emerging resistance

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## ABSTRACT

The ongoing problem of emerging antimicrobial resistance has been likened to a balloon where settling one specific issue results in a 'bulge' of even worse problems. However, much has been learned about how to best use our critical antibacterial agents in ways to avoid or even repair some of the resistance damage that has been done. A compilation of current literature strongly suggests that to slow the development of resistance to antimicrobial agents it is optimal to use drugs with more than one mechanism of action or target, to prescribe those with demonstrated ability to minimise or reverse resistance problems, and to avoid underdosing of potent antibiotics. The most recent information also indicates that it is best to limit empirical use of  $\beta$ -lactam plus fluoroquinolone combination therapy, since these two classes activate some common resistance responses, and using them together can facilitate multidrug resistance in important pathogens, particularly *Pseudomonas aeruginosa* and *Acinetobacter* species. This review discusses the role of each major antimicrobial class on resistance development and presents specific strategies for combating the growing problem of multidrug-resistant bacteria. We now have the knowledge to better manage our antimicrobial agent prescribing practices, but finding the will and resources to apply our understanding remains a formidable challenge.

**Keywords:** antimicrobial agent use, emerging resistance, review

*Clin Microbiol Infect* 2005; 11 (Suppl. 5): 4–16

## INTRODUCTION

The beginning of the 21st century has been accompanied by what appears to be an increasing number of emerging infectious diseases, some truly new, e.g., severe acute respiratory syndrome (SARS) [1], and others caused by old microbes possessing new resistance phenotypes (multi-drug-resistant *Pseudomonas aeruginosa* and *Acinetobacter* spp.) or toxin (community-acquired methicillin-resistant *Staphylococcus aureus* with the Panton–Valentine leukocidin toxin) genes [2–4]. It is as if we have passed through three distinct eras over the last 100 years—moving from the pre-antibiotic era through the antibiotic era and into the era of emerging infectious diseases. Many questions are worthy of consideration as we try to

understand why this is occurring, so as to better cope with infectious diseases on both the personal and global fronts. With very few new antimicrobial agents being introduced, and even fewer at the discovery stage, a critical question to ask ourselves is whether prescribing practice(s) can be improved to reverse, or at least retard, that portion of the emerging infections problem that is self-inflicted by suboptimal use of our available antimicrobial agents. The purpose of this review is to make a critical assessment of what can be gleaned from current evidence and suggest what might be practically done to slow the process of bacteria developing multidrug resistance. More than 10 years ago, Dr Harold Neu sounded the alarm over increasing antibiotic resistance [5]. In a recent report on the progress of pathogens, McGeer correctly points out that antibiotic pressure provides a crucial facilitative role in the dissemination as well as the development of resistance [6]. Thus, an important focus for better use of antimicrobial agents must be to assess the impact of major antibacterial classes on development of resistance

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to their related compounds, as well as to explore the impact that one class of antimicrobial agents may have on enhancing resistance to unrelated drugs.

## THE IMPACT OF RESISTANCE TO ANTIMICROBIAL AGENTS

This is a much-discussed and written-about topic, and the great majority of evidence indicates the importance of this healthcare issue. At the very least, published data clearly suggest that when people are admitted to the hospital with an antibiotic-resistant bacterial infection, they are much less likely to receive the proper initial therapy, and this is associated with a costlier hospital stay [7]. Considerable evidence also confirms that mortality rates are higher in patients not given early therapy active against their infecting microbe [8,9]. Some even consider the problem as a threat to our entire healthcare system [10].

## THE ORIGINS OF RESISTANCE TO ANTIMICROBIAL AGENTS

It is not surprising that bacteria can readily adapt to antibiotic exposure, since they have been in existence, and thriving, for at least 3.8 billion years [11]. An excellent schematic presentation of the emergence and spread of resistance can be found on the Dutch Working Party on Antibiotic Policy web-site [12]. Resistance clearly begins with antibiotic exposure, and even if only one or two bacterial cells survive they have the opportunity to develop into resistant strains. Subsequently, these newly resistant microbes can pass from person to person, amplifying to potentially epidemic proportions. The dissemination is facilitated by imperfect infection control practices and antimicrobial use in large numbers of people that permits resistant pathogen spread among persons with diminished protective normal flora. Thus, improving our use of antimicrobial agents provides at least two opportunities to better manage the emergence and spread of resistance. The first opportunity for improvement is to select drugs and dosing regimens that minimise the microbes' ability to survive and thus prevent the initial development of resistance. The second opportunity is to use agents that limit the spread of healthcare-associated infectious diseases and

microbial resistance, preventing what has come to be referred to as collateral damage. Considerable data are available on both aspects to facilitate the wise choice and use of antimicrobial chemotherapy.

## OPTIONS THAT CAN IMPROVE THE USE OF ANTIMICROBIAL AGENTS

Throughout the last few decades of antibiotic use, many ideas have arisen that can help practitioners to better prescribe these agents. These include the development of practice guidelines to improve treatment uniformity, controls or restrictions on what can be used based on expert decision-makers and economic factors, professional education, national guidelines by reputable policy-makers, and recommendations for prudent use through practices such as antibiotic step-down prescribing and cycling [10]. However, to date, none has had a noticeable impact on the problem at hand. For the future, improved diagnostics and information systems offer promise [13,14], but these are still some years away. During the last decade, much information has appeared in the medical literature regarding the impact of specific drugs and/or classes on the emergence, dissemination and, occasionally, reversal of problems relating to antibiotic resistance and the spread of healthcare-associated pathogens. Using this information can help us to enhance effective prescribing and limit the ongoing development and spread of microbial resistance. Additionally, through the field of pharmacodynamics, we have learned much on how the actual administration of antimicrobial agents can be either beneficial or detrimental, and this knowledge can be applied today.

## LESSONS FROM NATIONAL SURVEILLANCE PROGRAMMES

In the late 1990s, Austin *et al.* published an article that modelled the rise of antibiotic resistance and the scope of remedies needed to reverse the problem, with validation based on observations in Finland and Iceland [15]. Their core finding was that for each drug or drug class there is a level of use that, once exceeded, will eventually lead to resistance. Once this occurs, dramatic reductions in drug prescribing are needed to reverse the trend towards increasing resistance. In general, it

appeared that once use exceeded 15–25 defined daily doses (DDD) per 1000 patients in a population, resistance would typically occur at some time-point. To reverse this, a major reduction in use, as much as 50% or more, to achieve levels below the antimicrobial agent's resistance threshold (generally no more than 25 DDD/1000 patients) would be needed. For hospital settings, the usual denominator used is 1000 patient-days. If one assumes that the typical course of antibiotic therapy is 10 days, then 25 DDD/1000 patient-days can be converted to 2.5% of patients receiving a given drug (or drug class) in the hospital or nursing unit at any given time—an exceedingly small amount in today's healthcare environment.

Reviewing recent reports on national antimicrobial consumption and accompanying resistance problems is an instructive first step for understanding current resistance trends. In 2003, Neuhauser *et al.* reported a large investigation that recorded changes in bacterial susceptibility in intensive care units (ICUs) across the USA [16]. Between 1994 and 2000, they recorded susceptibility results for nearly 36 000 Gram-negative bacilli along with the consumption of fluoroquinolones in the geographical area surrounding the participating hospitals. The administration of fluoroquinolones increased by 147% and the observed increases in resistance to various agents were: 10% to quinolones, 6% to gentamicin, 3% to ceftazidime and ampicillin–sulbactam, 2% to cefotaxime, ceftriaxone and ticarcillin–clavulanate, 1% to imipenem, and 0% to piperacillin–tazobactam. This would suggest that a threshold had been reached for fluoroquinolone use, and the over-prescribing of this class was increasing resistance in many Gram-negative bacteria to all the fluoroquinolone agents.

Information regarding antibiotic use and bacterial resistance in The Netherlands is also enlightening [12]. Between 1997 and 2001, the use of amoxicillin–clavulanate rose from 143 to 169 DDD/1000 patient-days, which represents a very high level of use based on Austin's calculations [12,15]. Fluoroquinolone use also increased, from 40 to 49 DDD/1000 patient-days. Interestingly, significant increases in resistance were only seen for fluoroquinolones in *Klebsiella pneumoniae*, *P. aeruginosa*, *Escherichia coli* and *S. aureus*, and for macrolides in *S. aureus* and *Streptococcus pneumoniae* [12]. The authors noted that in the preceding 5 years the use of macrolides and fluoroquinolones

in The Netherlands's hospitals had doubled. These data suggest that the threshold for increasing fluoroquinolone and macrolide resistance had been surpassed here as well. Also of note, from the aspect of minimising multidrug resistance development, is the observation that the amount of extended-spectrum cephalosporin non-susceptibility for *E. coli* in The Netherlands remained at less than 2% during 2003 [17], one of the lowest levels in all of Europe. This raises the possibility that use of  $\beta$ -lactamase-stabilised antibiotics such as amoxycillin–clavulanate, the most commonly used injectable agent in The Netherlands' hospitals, may not be as prone to facilitate the emergence and/or spread of resistance as compounds in the fluoroquinolone and macrolide classes.

A third study, from the UK, assessed any changes in piperacillin–tazobactam activity 9 years after this drug was introduced. There was no change in activity against *P. aeruginosa* (95% susceptible) or *Proteus* spp. during the 9 years, but some problems were detected: resistance rose in *E. coli* from 4% to 10%, in *Klebsiella* spp. from 5% to 21%, and in AmpC-inducible Enterobacteriaceae from 17% to 23% [18]. However, no information concerning drug use was provided, so it is difficult to assess what agent(s) may have been responsible for these changes.

As a final example, national antimicrobial agent (injectable) usage data are available for Malaysia. During 2002, some 62% of administered antibiotics were extended-spectrum cephalosporins, another 13% were of the carbapenem class and 7% were fluoroquinolones (data obtained from the IMS Retail and Provider Perspective. Plymouth Meeting, PA, USA). The major problem reported for ICU patients is infection with cephalosporin-resistant *Acinetobacter* spp., representing nearly 50% of isolates. Nearly 33% of *Klebsiella* spp. strains and 8% of *E. coli* are also resistant to extended-spectrum cephalosporins [19]. Importantly, of the total injectable antibiotic given, 17% was cefoperazone–sulbactam, which is recommended for use at a very low dosage of 1–2 g every 12 h [20,21]. A lead article written 20 years earlier demonstrated that for cefoperazone to be adequately dosed to achieve the standard susceptibility breakpoint of 16 g/L the administered active drug must be given at a dose of between 2 and 3 g every 6 h [22]. This information

suggests that predominant use of broad-spectrum cephalosporins, particularly when potent entities are given at very low doses, has a strong potential to facilitate the emergence of many bacterial strains resistant to this entire class of antimicrobial agents.

There is considerable variation in the use of antimicrobial agents across the world and even within geographical areas with close social and economic ties, such as the European Union [23]. In order to start devising a plan for altering prescribing practices, one first needs to know what problems are being faced locally, as only then can a rational plan for improvement be developed, and the necessary implementation on the part of prescribing physicians be achieved. What follows is the evidence from the recent literature as to what agents and classes of drugs contribute to the emergence and spread of resistance, accompanied by examples of what has worked in clinical practice to stabilise or reverse the problem. Basic science is also adding to our understanding of why certain chemical compounds may be more problematic, and this will be commented upon whenever appropriate.

## IMPACT OF USING SPECIFIC CLASSES OF ANTIMICROBIAL AGENTS

There are a limited number of antimicrobial drug classes used for treatment of infectious diseases within the hospital setting. These include aminoglycosides, carbapenems, cephalosporins, fluoroquinolones, penicillins, and vancomycin, and there is also growing application of the new compounds linezolid and quinupristin-dalfopristin, which are reserved for specific, limited indications. It is instructive to review the applicable experience concerning the impact of using each of the therapeutic classes.

### Aminoglycosides

Aminoglycosides have been available since the early onset of the antibiotic era, with streptomycin reported in 1944 [24]. Resistance is mediated by several mechanisms, ranging from efflux to impaired uptake to target modification and enzymic inactivation [24]. However, there is little evidence that the aminoglycosides mediate resistance to other drug classes. Even when impacted

by resistance themselves, these drugs are well-known for their capacity to exhibit synergistic activity with cell wall-active agents [24].

In 1991, Gerding *et al.* reported their experience with rotation, or cycling, of gentamicin and amikacin to manage the problem of emerging resistance in Enterobacteriaceae against gentamicin. In each of the cycles, they were able to switch use of gentamicin from between 50 and 100 DDD/1000 patient-days to fewer than 5, a ten-fold decrease, and over amikacin cycle periods of 2 years they saw the desired change of increased susceptibility to gentamicin [25]. From what they report, the only observed effect was on the aminoglycoside susceptibility of the hospital's bacteria. Similar results were obtained from a comparable study done in Belgium [26]. A large, additional evaluation of aminoglycoside prescribing in 14 US hospitals also provided findings consistent with those of Gerding *et al.*, with a switch to amikacin providing improved aminoglycoside activity against Gram-negative pathogens, including *P. aeruginosa*, *Klebsiella*, *Serratia*, and *Proteus* spp. [27]. This experience indicates little impact of the aminoglycosides on the susceptibility of bacteria to other agents, but a clear effect of drug consumption and resistance within their own class of antibiotics. It also shows that for the problem of significant resistance to gentamicin or tobramycin, changing (cycling) to amikacin for up to 2 years can re-establish susceptibility to the aminoglycosides.

### Carbapenems

Imipenem and meropenem are considered by most to be the two agents with the widest antibacterial spectrum of any available antibiotic class, due to their considerable  $\beta$ -lactamase stability [28]. Early on it was recognised that permeability-mediated resistance was important for the carbapenem class, particularly for organisms such as *P. aeruginosa* and *Acinetobacter* spp. [28]. Zinc-dependent carbapenemases are potent inactivating enzymes mediating resistance to the carbapenems, but to date have remained of limited importance, because of their presence in only a few bacterial species [28].

Despite the very broad spectrum of activity of this antibiotic class, the initial publication associating a 'balloon concept' with antibiotic resistance arose from a study in which imipenem was

substituted for cephalosporins in order to reduce the rate of occurrence of cephalosporin-resistant *K. pneumoniae* [14,29]. Rahal *et al.* were able to reduce ceftazidime use by 73% and cefotetan use by more than 95%, but this was accompanied by a 140% increase in imipenem prescribing. While the authors' efforts succeeded in reducing the occurrence of cephalosporin-resistant *Klebsiella* spp. by 44%, they observed a 69% increase in imipenem-resistant *P. aeruginosa* within their medical centre [29]. Burke argued that the improvement in activity against *Klebsiella* spp. may have pushed the antibiotic balloon and resulted in an outcome with more resistance in *P. aeruginosa*, giving an overall result less helpful than desired [14].

The major current problem in the use of the carbapenem antibiotics constitutes highly resistant Gram-negative pathogens represented by *P. aeruginosa* and *Acinetobacter* spp., both of which encompass multiple modes for developing resistance [2]. The most important mechanism is probably that of upregulated efflux, particularly when associated with loss of outer-membrane (permeability) proteins such as the porin OprD. Complicating resistance to this class is the fact that OprD is co-regulated by the efflux system MexEF–OprN, which can be selected by fluoroquinolones [2]. When such a selection is generated by a fluoroquinolone, even without exposure to a carbapenem, the strain of *P. aeruginosa* will be resistant to the fluoroquinolones and imipenem, and also have reduced susceptibility or resistance to meropenem. The increasing number of acquired carbapenemases being found in *P. aeruginosa* and *Acinetobacter* spp. will only add to the growing carbapenem resistance problem [30].

When *Acinetobacter baumannii* becomes resident in a healthcare setting, an important risk factor for acquisition of a carbapenem-resistant strain is treatment with one of these agents [31,32]. Also, once carbapenem-resistant *Acinetobacter* spp. are present in a region, these bacteria have a propensity to spread throughout the geographical area [33]. Overall, the data support the conclusion that carbapenems are susceptible to fairly rapid resistance development and lead to the spread of carbapenem-resistant strains of *P. aeruginosa* and *A. baumannii* when frequently used in the clinical setting. With high-level use, resistance can also occur in other genera, such as *Citrobacter* spp. [34]. As will be discussed in detail later, there is also

the strong implication that fluoroquinolones select for joint quinolone–carbapenem resistance in these microbial genera, thus contributing to the problem of carbapenem and multidrug resistance in both *P. aeruginosa* and *Acinetobacter* spp. The recent data from the National Nosocomial Infections Surveillance (NNIS) system highlight the problem of increasing carbapenem resistance in *P. aeruginosa* [35]. The pooled mean carbapenem use in non-ICU inpatient areas between January 1998 and June 2003 was 5.9 (ranging from 0.4 to 14.8) DDD/1000 patient-days, while in these same care areas the mean fluoroquinolone use was 68.3 (ranging from 24.8 to 177.0) DDD/1000 patient-days. Despite the fact that the use of carbapenems was well below that expected to engender the emergence of resistance, 12.4% (range 5.2–20.6%) of *P. aeruginosa* strains were resistant to imipenem. Not surprisingly, an average of 27.2/29.4% (range 12.9/14.2% to 42.9/44.7%) of these same isolates were also resistant to ciprofloxacin–levofloxacin [35]. This information strongly reinforces the concept that carbapenem resistance in microbes such as *Acinetobacter* spp. and *P. aeruginosa* is most likely caused by overuse of fluoroquinolones, which upregulate efflux systems that export both quinolones and carbapenems [36].

### Extended-spectrum cephalosporins

The extended-spectrum cephalosporins have come to be used in a wide variety of clinical settings. The currently available agents penetrate cerebrospinal fluid and have significant advantages over past treatments for bacterial meningitis. They are considered to have good clinical efficacy as well as a low rate of side-effects, and thus have become the agents of choice for many infectious diseases [37]. The bacterial responses to exposure to agents that are active against the key synthetic pathways for cell wall synthesis are multifaceted. Bacteria, particularly Gram-negative bacilli, produce both chromosomal and plasmid-mediated resistance enzymes ( $\beta$ -lactamases) that are continually growing in number and phenotypic expression [30,38,39]. For bacteria such as *P. aeruginosa* and *Acinetobacter* spp., limiting drug penetration through shedding of porins and upregulating efflux pumps is complementary to  $\beta$ -lactamase production and leads effectively to high levels of resistance, much as is seen for the carbapenems. It is likely that this combined mechanism is

important for most Gram-negative bacteria to a lesser or greater extent. *Acinetobacter* spp. are also naturally competent and can remodel their target sites as an added resistance mechanism [30,38,39].

In US hospitals, the extended-spectrum cephalosporins appear to be the most frequently prescribed antimicrobial agents, with an average of 93.7 DDD/1000 patient-days used in non-ICU areas, and mean use in the ICU setting ranging from 122.4 to 327.9 DDD/1000 patient-days. With this extremely high level of use, it is not surprising that in the ICU setting resistance to *P. aeruginosa* and *Enterobacter* spp. has reached 13.8% and 26.6%, respectively [35]. Even with inconsistent screening for extended-spectrum  $\beta$ -lactamase (ESBL) production, resistance in *K. pneumonia* now exceeds 5% [35]. The directly related consequences of excessive use of these agents are indicated by growing problems with ESBL-producing Enterobacteriaceae [40] and *A. baumannii* resistant to multiple antibiotic classes [32,41]. Unfortunately, use of extended-spectrum cephalosporins has also become associated with 'collateral damage' by facilitating infections due to methicillin-resistant *S. aureus* (MRSA) [42] and vancomycin-resistant enterococci (VRE), with one association linked to ticarcillin-clavulanate, which behaves in this setting like a cephalosporin with no activity against enterococci [43–45]. The persistent problem of *Clostridium difficile*-associated diarrhoea (CDAD) is also related to cephalosporin prescribing [46–48], with benefit from lowering cephalosporin use having been demonstrated [49].

### Extended-spectrum penicillins

The penicillins that have received the most attention in recent research trials are those comprising the group of combination agents where part of the antibiotic includes a  $\beta$ -lactamase inhibitor drug such as clavulanate, sulbactam or tazobactam. In addition to being potent inhibitors of Ambler class A (plasmid-mediated)  $\beta$ -lactamases [30,38,39], they have been shown to contribute additional effects by binding to accessory penicillin-binding proteins, the key targets of penicillin compounds. These additional properties include enhanced killing of MRSA (compared to vancomycin) in an in-vivo animal model [50], better in-vitro bactericidal activity against Gram-negative and Gram-positive

bacteria [51] and augmented intracellular killing of non- $\beta$ -lactamase-producing bacteria by neutrophil leukocytes [52]. With this evidence for the multifactorial action of  $\beta$ -lactam/ $\beta$ -lactamase inhibitor compounds in mind, it is not surprising that they are becoming recognised as very important agents in the battle against emerging resistance.

Clinical use of these agents presents the best evidence for their role in combating bacterial resistance. As noted earlier, use in The Netherlands has been high, but has not been accompanied by increasing resistance development [12]. However, most importantly, many investigators have demonstrated the utility of using these compounds to reverse problems with ESBLs, VRE and CDAD. While not extensively studied, use of these agents may even help to better manage the increasing prevalence of MRSA [53], as evidenced by the fact that the first patient infected with vancomycin-insensitive MRSA was actually cured by administration of ampicillin-sulbactam [54].

The most extensive published clinical experience concerns the substitution of one of these agents for an extended-spectrum cephalosporin to reduce the prevalence of ESBL-producing bacteria [53,55–61]. Two of these studies are particularly worth highlighting. The first, by Peña *et al.*, replaced third-generation cephalosporins with imipenem-cilastatin and piperacillin-tazobactam, and showed that once they were able to maintain cephalosporin use below 25 DDD/1000 patient-days, the rate of ESBL-producing bacteria fell from 40% to 0% [56]. The second study, by Bantar *et al.*, used piperacillin-tazobactam to replace third-generation cephalosporins as an intervention to reduce the high level of ESBL-producing *K. pneumoniae*, in a setting where a prior switch to cefepime had failed to provide the desired effect [61]. They lowered ceftazidime and ceftriaxone use from 17.8 to 1.1 DDD/1000 patient-days and 12.7–5.7 DDD/1000 patient-days, respectively, whereas the overall prescribing of piperacillin-tazobactam rose from 0 to 30.6 DDD/1000 patient-days. The rate of ESBL-producing *K. pneumonia* dropped from 68% to 37%, and interestingly, the resistance in *P. aeruginosa* against piperacillin-tazobactam also fell, from 11% to 6%, despite heavy use of that agent [61].

The impact of using  $\beta$ -lactamase inhibitor compounds has also been investigated in the

management of VRE, in a study that is the only published investigation of antibiotic cycling dealing with Gram-positive pathogens [62]. In this most interesting intervention, Bradley *et al.* replaced ceftazidime with piperacillin-tazobactam, and then cycled back to ceftazidime use. They also accompanied their antibiotic intervention with an enhanced infection control programme. By implementing both an expanded infection control programme and replacing extended cephalosporin use with a  $\beta$ -lactamase inhibitor drug, they reduced the rate of colonisation with VRE from 57% to 8%, and in doing so completely eliminated all clinical infections. However, upon the switch back to ceftazidime, the rate of colonisation with VRE rose to 36% and clinical infections reappeared in patients cared for on the nursing unit [62]. It is also noteworthy that the increase in colonisation with VRE and the return of clinical infections with this multidrug-resistant pathogen only took 4 months after the switch back to ceftazidime, implying that a cycling strategy to minimise problems with this microbe is not useful. Supporting this prospective trial are observational studies such as that by Donskey *et al.*, who demonstrated a protective effect against acquisition of VRE with receipt of ampicillin-sulbactam or piperacillin-tazobactam vs. an increased risk of infection with administration of cephalosporins and ticarcillin-clavulanate [44]. Results similar to those of Bradley *et al.* were reported in the more recent article by Kolar *et al.* [63].

The final context in which a prospective clinical trial demonstrates the utility of  $\beta$ -lactamase inhibitor compounds in managing health-care-associated infectious diseases is that of CDAD. Settle *et al.* performed a well-designed crossover study comparing the impact of cefotaxime and piperacillin-tazobactam use on the prevalence of this very important healthcare pathogen [64]. They demonstrated a statistically significant reduction in both colonisation and infection for the piperacillin-tazobactam arm of the study, with rates of colonisation nearly four-fold lower with piperacillin-tazobactam, and those of infection reduced by nearly ten-fold, compared to cefotaxime [64]. Importantly, this trial is supported by a large retrospective observational investigation demonstrating the low association of ticarcillin-clavulanate with the development of CDAD (0 cases in nearly 62 000

doses administered) as compared to extended-spectrum cephalosporins (51 cases for some 40 000 doses given), thus demonstrating the risk associated with receiving a cephalosporin vs. a  $\beta$ -lactamase inhibitor combined compound [65]. The results of Settle *et al.* are further reinforced by the experience of Wilcox *et al.*, who changed from cefotaxime to piperacillin-tazobactam use, and then back to cefotaxime when the inhibitor combination became temporarily unavailable [66]. During the initial switch when cefotaxime use was curtailed, CDAD rates fell by over 50%, and with the re-introduction of cefotaxime they rose by 232% [66], once again supporting the replacement of cephalosporin prescribing with piperacillin-tazobactam as an effective strategy to reduce the overall burden of CDAD.

### Fluoroquinolones

Fluoroquinolones are some of the most important antimicrobial agents that we have for treatment of serious infections. They act directly on the bacterial chromosome with lethal effect on microbial replication processes [67,68]. Unfortunately, their overuse is now associated with a myriad of emerging resistance consequences, some directly affecting the fluoroquinolone class [16], and others impacting on resistance and emerging infections in unanticipated ways. One of the recently recognised critical mechanisms of resistance is that resulting from induction of efflux-pump activity. It is now known that fluoroquinolones can select for mutants of Gram-negative bacteria that overproduce a wide variety of efflux pumps and in a single step cause resistance to practically all classes of antimicrobial agents [9,69]. A growing concern is the problem apparently caused by heavy use of these agents in association with increasing resistance to other agents, such as carbapenem resistance in *P. aeruginosa* [70,71]. Since fluoroquinolones can turn on several multidrug-efflux systems that also affect carbapenems [70,71], heavy use of these agents in hospitals can facilitate the development of multidrug-resistant *P. aeruginosa* and leave little available therapy for treatment of these infections. A recent matched case-control study investigating the role of antimicrobial therapy in acquisition of multidrug-resistant *P. aeruginosa* supports the in-vitro science implicating prior receipt of a fluoroquinolone as the major

independent risk factor for the emergence of these pathogens [72]. This accumulating evidence indicates that it is best to avoid the use of fluoroquinolones and  $\beta$ -lactams as a combination for empirical therapy of serious infection. If one begins treatment with a  $\beta$ -lactam plus an aminoglycoside (when two agents are desirable) for the first 48–72 h, and either discontinues the aminoglycoside if cultures are negative, or changes to specific therapy once the organism identification and susceptibility are known, then a significant reduction in fluoroquinolone use can be achieved, with little risk of aminoglycoside nephrotoxicity or the need for therapeutic drug monitoring [73,74].

Fluoroquinolones, like other antimicrobial agents, directly influence the level of resistance to themselves in many bacterial species, as evidenced in large surveillance studies of the last few years [16,75,76]. We demonstrated in 1998 that introduction of a second agent in the quinolone class to the hospital setting was accompanied by increased prescribing and rapidly led to increasing fluoroquinolone resistance in *P. aeruginosa* [77]. Importantly, with withdrawal of the less active agent and lowering of overall use, it was possible to achieve a reversal of the resistance trend [77]. Supporting our finding is the recent report by Paladino *et al.*, who demonstrated that treatment with a weaker-potency fluoroquinolone predisposed to later infection with quinolone-resistant *P. aeruginosa* [78]. Some of the newer fluoroquinolone agents are less susceptible to efflux than are the older compounds [79,80], and it remains to be learned if preferential use of agents such as moxifloxacin, especially against Gram-positive pathogens, can slow the future development of resistance against this important antimicrobial class.

One of the current major concerns arising from the use of fluoroquinolone antimicrobial agents is the concept of 'collateral damage', or the enhanced spread of drug-resistant pathogens that at first glance do not seem to be associated with administration of the offending compound(s). In addition to the concern that these agents can cause resistance to  $\beta$ -lactams in Gram-negative bacteria, there are recent reports linking the spread of MRSA to fluoroquinolone prescribing [81–83], and an increased prevalence of CDAD linked to use of levofloxacin and gatifloxacin [85–87]. Harbarth *et al.* found that prior receipt of a

fluoroquinolone was an independent risk factor for persistence of MRSA carriage and failure of mupirocin decolonisation, even in the absence of high-level mupirocin resistance [81]. Graffunder and Venezia also reported that quinolone (levofloxacin) exposure was independently associated with MRSA infection (odds ratio = 8.01) in a large case-control study of 121 patients [82]. Similar findings were recently described by Weber *et al.* [83]. These investigators even suggested a mechanism that can facilitate MRSA colonisation after exposure to fluoroquinolones. They recalled that Bisognano *et al.* demonstrated that ciprofloxacin exposure leads to increased expression of adherence factors promoting host colonisation with *S. aureus* [84]. Significant changes in adhesion were exhibited when strains were grown in the presence of 1/4 MIC of the quinolone, a level of exposure that would be expected in the case of MRSA, since MRSA strains are now largely resistant to all available fluoroquinolones [83]. This concept could also explain the persistence of colonisation noted earlier by Harbarth *et al.* [81].

CDAD has recently come to be associated with fluoroquinolone prescribing. McCusker *et al.* found the greatest association with levofloxacin prescribing, while Gaynes *et al.* tracked an outbreak to a switch from levofloxacin to gatifloxacin use [85,86]. In his editorial, Gerding implicated all fluoroquinolone (over)use as causing emerging resistance in yet another microbial pathogen, *C. difficile*, this in turn leading to spread of this organism among patients within the hospital environment [87]. It is clear that high levels of fluoroquinolone use can lead to several different adverse consequences, and that only through careful surveillance to detect problems, and thoughtful planning to deal with them, can healthcare providers effectively manage these consequences.

### Vancomycin

Vancomycin is a naturally occurring antibiotic that has been marketed for over 40 years [88]. The agent is considered to be bactericidal to most Gram-positive bacterial species, but to have no activity against Gram-negative pathogens, because of its bulkiness. The action of this antimicrobial agent involves blocking synthetic enzyme access to the acyl-D-ala-D-ala portion of the peptidoglycan precursor, thus stopping



completion of the cell wall structure [88]. The main resistance to vancomycin is directly related to its use, and was very slow to emerge; it required nearly 30 years after the 1958 launch of vancomycin for the first vancomycin-resistant enterococci to appear [89]. There does not appear to be any impact on other antimicrobial classes associated with the use of vancomycin.

### New antimicrobial agents

The newest injectable antimicrobial classes are the oxazolidinones, represented by linezolid [90], and the streptogramins, of which quinupristin–dalbapristin is currently the only available member [91]. These compounds are too new on the therapeutic scene for any adverse resistance implications resulting from their use or overuse to have been determined. However, if history is to be a teacher for us, we will need to remain vigilant and watch for unexpected consequences

of the introduction of these welcome new compounds.

### THE ROLE OF APPROPRIATE ANTIMICROBIAL AGENT DOSING IN MINIMISING EMERGING RESISTANCE

The primary goal of antibiotic treatment is to cure the patient of infection, with avoiding resistance being secondary (at best) in the mind of the prescribing physician [92]. Over the last decade we have learned much about the theoretical and practical pharmacodynamic approaches to prescribing that can help achieve this first goal [93,94]. For example, it is clear that the ratio of peak drug concentration to the MIC for the infecting pathogen maximises bacterial killing for aminoglycosides, and therefore most dosing is now done as a single daily administration [95,96]. We also now understand that the ratio of

**Table 1.** Recommendations (with ratings<sup>a</sup>) for management of antimicrobial agent resistance

Problem	Useful solution	Rating	References
1. High level <sup>b</sup> of carbapenem-resistant <i>P. aeruginosa</i>	Reduce <sup>c</sup> fluoroquinolone and/or carbapenem use	BIII	[2,9,35,69–72]
2. High level of fluoroquinolone-resistant <i>P. aeruginosa</i>	Reduce fluoroquinolone use and change primary drug to ciprofloxacin	AI	[9,16,67,69,75–78]
3. High level of carbapenem-resistant <i>A. baumannii</i>	Reduce carbapenem use and assess for clonal problem	AII	[31–33]
4. High level of $\beta$ -lactam resistance in <i>P. aeruginosa</i>	Reduce extended-spectrum cephalosporin use and replace with piperacillin–tazobactam	BIII	[35]
5. High level of ESBL-producing Enterobacteriaceae	Reduce extended-spectrum cephalosporin use and replace with piperacillin–tazobactam or imipenem–cilastatin or ampicillin–sulbactam	AI	[29,53,55–61]
6. High level of gentamicin–tobramycin resistance in Enterobacteriaceae	Replace with amikacin	AI	[25–27]
7. Concern over presence of VRE	Reduce cephalosporin and fluoroquinolone use and replace with piperacillin–tazobactam	AI	[43–45,62,63]
8. Concern over presence of MRSA	Reduce cephalosporin and fluoroquinolone use, and replace with a $\beta$ -lactamase inhibitor drug	BIII	[50,53,54,81–84]
9. Concern over presence of <i>C. difficile</i>	Reduce cephalosporin, clindamycin and fluoroquinolone use and replace with: (a) piperacillin–tazobactam or (b) ticarcillin–clavulanate	AI and BIII, respectively, for (a) or (b)	[49,64–66,85–87]

ESBL, extended-spectrum  $\beta$ -lactamase; VRE, vancomycin-resistant enterococci; MRSA, methicillin-resistant *Staphylococcus aureus*.

<sup>a</sup>Ratings follow the convention recommended by the Infectious Diseases Society of America for the evidence to support each recommendation [99].

<sup>b</sup>High level indicates resistance exceeding 10% of recovered strains.

<sup>c</sup>A reduction is represented by a lowering of prescribing by at least 50% (based on defined daily doses (DDD)/1000 patient-days) with a goal of using less than 15 DDD/1000 patient-days of the likely offending agent. (Note: If use when the problem is detected is below 15 DDD/1000 patient-days, then the affected agent/class is not likely to be responsible for the resistance problem.)

the 24-h area under the serum concentration curve (AUC) and the MIC is related to successful therapy with fluoroquinolones, macrolides, ketolides and glycopeptides; and that the time above the MIC best predicts treatment success for  $\beta$ -lactams, tetracycline and oxazolidinones. This understanding must be applied not only to patients, but also to our overall prescribing and stewardship of these important drugs in the battle against facilitating resistance. As an example, when potent agents such as cefoperazone-sulbactam are routinely prescribed at less than one-quarter the required dose for Gram-negative pathogens in areas such as Malaysia [20–22] and India (author's unpublished data), it is not surprising that very high levels of multidrug-resistant pathogens emerge [19,97,98], and this practice should not be tolerated by physicians or encouraged by the pharmaceutical industry.

## SUMMARY

Much useful information on how to limit, avoid and even reverse resistance to antimicrobial agents has become available over the last decade. The bulk of the literature appears to suggest several critical options. An important first step is to perform local surveillance so as to understand what problems are being faced in one's own practice area. Once the problems are recognised, there are now well-evidenced steps that can be taken to slow, or even reverse, the development of resistance. Table 1 lists the current most important resistance problems along with potential solutions, each documented by ratings as to how well the proposed intervention has been investigated. The ratings follow the recommendations developed by the Infectious Diseases Society of America for such a guideline [99], and the ratings used are explained in Table 2. In general, based on this review, to slow the development of resistance to antimicrobial agents, the current literature strongly suggests that we use agents with more than one mechanism of action or target, use agents with demonstrated ability to minimise resistance, avoid combining  $\beta$ -lactams and fluoroquinolones for empirical therapy against Gram-negative pathogens, and avoid underdosing of potent antibiotics.

In conclusion, we have now had some 50 years of experience in prescribing antimicrobial compounds and much insight has been gained, as

**Table 2.** Rating guide for recommendations contained in Table 1 (adapted from the guideline developed by the Infectious Diseases Society of America [99])

Strength of recommendation
A. Good evidence to support a recommendation
B. Moderate evidence to support a recommendation
C. Poor evidence to support a recommendation
Quality of evidence
I. Evidence from at least one properly designed, prospective clinical trial as well as additional corroborating retrospective analyses
II. Evidence from more than one cohort or case-controlled analytical study or from multiple time-series; these may be supported by results from uncontrolled observations
III. Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

described above. At this point in our use of antimicrobial drugs, McGeer's quote from Goethe seems most appropriate [6]:

*Knowing is not enough; we must apply.*

*Willing is not enough; we must do.*

The future of infectious disease management is up to each of us!

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